

## Drug resistance in *Mycobacterium tuberculosis*: a survey over 25 years in Blackburn

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**ABSTRACT** Over the past 25 years the incidence of tuberculosis in Blackburn has changed from one that was below the national average to one which is consistently in the 10 highest local authority areas in England and Wales. A survey of primary and acquired drug resistance over the same period included 974 ethnic white patients and 538 of Indian subcontinent ethnic origin. Primary drug resistance in the white population has fallen consistently from 1965 onwards and is now zero. Only one case of acquired resistance has occurred in the last five years. Primary resistance in the immigrant community has been 11-15% from 1965 onwards, and five cases of acquired resistance have occurred since 1970. The pattern of drug resistance over this period supports the view that there is no evidence of cross infection between the native white and immigrant ethnic groups.

There have been few surveys of drug resistance in *Mycobacterium tuberculosis* over the last 25 years in the United Kingdom. Since the first national survey in 1955-6<sup>1</sup> there have been only four short cross sectional national surveys of drug resistance. The second national survey<sup>2</sup> of 1963 covering eight months, the 1978-9 Medical Research Council (MRC) Tuberculosis and Chest Diseases Unit's survey<sup>3</sup> covering six months, and the 1983 survey by the MRC unit,<sup>4</sup> again covering six months, looked at primary resistance. The 1961 British Tuberculosis Association survey (BTA)<sup>5</sup> looked at acquired resistance over six months, and also included a control group for primary resistance.

Over the last 25 years, although there has been a considerable fall in tuberculosis in general, the pattern of the disease has changed considerably, the contribution of the Indian subcontinent ethnic group having risen from under 16.5% overall in 1965<sup>6</sup> to 36% by 1983.<sup>4</sup> Tuberculosis in the Blackburn local government area of the Blackburn, Hyndburn and Ribble Valley District Health Authority over the last 25 years has changed from an incidence below the national average to an incidence consistently in the top 10 highest local government areas of England and Wales (fig). Over this period the Indian subcontinent

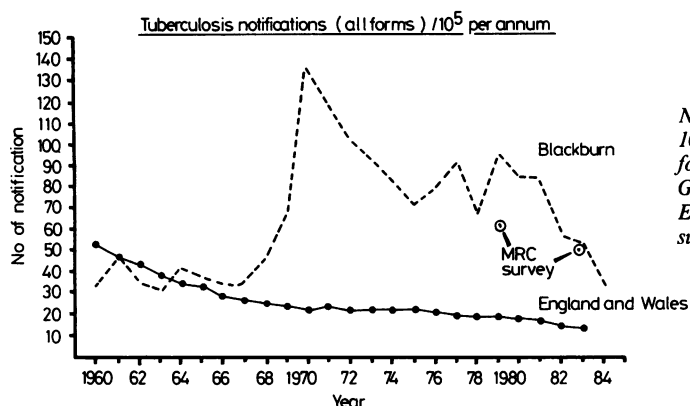
community has risen from 0.35% of Blackburn County Borough (population 106 242) in 1961<sup>8</sup> to 4.76% of 101 815 in 1971,<sup>9</sup> and to an estimated 11.5% of Blackburn Borough (population 141 928) in 1981.<sup>10</sup> Notifications from the Blackburn local government area supply over 80% of the total notifications within the district health authority. We report a longitudinal survey of drug resistance over 25 years in a single health authority.

### Methods

Records of all isolations of mycobacteria within the district health authority since 1960 have been kept by one of us (JMH). Only patients with isolates of *M. tuberculosis* were assessed. Duplicate isolations were eliminated, and the few patients whose treatment failed repeatedly were dealt with by including them once (the first time) in each five year period. The patients were divided into white and immigrant (Indian subcontinent) ethnic groups. The ethnic origin of immigrants was determined by place of birth if they were born outside the UK, or by place of birth of parents if they were born in the UK. The patients were also divided into those whose tuberculosis was newly diagnosed and those previously treated. Resistance to one or more antituberculous drugs in the first isolate from newly diagnosed patients was recorded as primary. Drug resistance in isolates of previously treated patients whose initial strains had been fully sensitive to all drugs was recorded as acquired resistance.

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Notifications of tuberculosis (all forms) per 100 000 population per annum for Blackburn and for England and Wales. Sources: 1960–70, Gardner *et al*<sup>7</sup>; 1978–9 and 1983, estimates for England and Wales, Medical Research Council surveys.<sup>3,4</sup>

From 1960 to 1971 initial drug sensitivity testing was carried out locally. The strains were tested for their sensitivity to streptomycin, *p*-aminosalicylic acid, and isoniazid by a standard resistance ratio method, *Mycobacterium tuberculosis* H37Rv being used as the standard reference strain. A resistance ratio of 1 was reported as fully sensitive, a ratio of 2 as borderline, a ratio of 4 as resistant and a ratio of 8 or more as highly resistant. Only those strains reported as resistant by the local laboratory were then forwarded to the Mycobacterium Reference Unit at Cardiff for confirmation of the drug resistance. The results reported are those confirmed by the Mycobacterium Reference Unit.

From 1972 onwards, after initial isolation locally, identification and sensitivity tests on all mycobacterial isolates was carried out by the Mycobacterium Reference Unit at Cardiff. This laboratory also uses a standard resistance ratio method as

above. *Mycobacterium bovis* is differentiated from *M. tuberculosis* in the Mycobacterium Reference Unit by differences in sodium pyruvate preference and niacin production, the presence of microaerophilic culture on depth medium, and the presence of pyrazinamide resistance. In this paper drug resistance ratios 1 and 2 are regarded as indicating sensitivity for the purposes of treatment. Strains shown in the tables as resistant are those with resistance ratios of 4 or more.

## Results

From 1960 to 1984 1512 patients had isolates of *M. tuberculosis* reported. These were divided according to ethnic group, 974 patients being white and 538 being immigrants from the Indian subcontinent. The incidence of drug resistance in the two groups is shown for each five year period in tables 1 and 2 for

Table 1 Primary and acquired resistance in 974 white patients

Period	Newly diagnosed patients		Previously treated patients	
	Tested	No (%) resistant	Tested	No (%) resistant
1960–4	341	33 (9.7)	28	16 (57.1)
1965–9	184	16 (8.7)	45	21 (46.7)
1970–4	147	7 (4.8)	14	7 (50.0)
1975–9	124	5 (4.0)	3	1 (33.3)
1980–4	81	0 (0)	7	1 (14.3)

Table 2 Primary and acquired resistance in 538 immigrant patients

Period	Newly diagnosed patients		Previously treated patients	
	Tested	No (%) resistant	Tested	No (%) resistant
1960–4	38	1 (2.6)	—	—
1965–9	87	12 (13.8)	—	—
1970–4	165	23 (13.9)	3	1 (33.3)
1975–9	136	15 (11.0)	7	2 (28.6)
1980–4	99	15 (15.2)	3	2 (66.7)

white and immigrant patients respectively. The pattern of primary resistance for the white group is given in table 3, and for the immigrant group in table 4. Acquired resistance in white patients is shown in table 5. Thirteen isolations of *M bovis* (10 from white and three from immigrant patients—all fully sensitive to first line drugs) and four isolations of *M kansasii* (white, smear positive with cavitary disease) have been excluded.

## Discussion

The 1955–6 national survey<sup>1</sup> showed an overall primary resistance in 4.5% of patients, with greater resistance to *p*-aminosalicylic acid and streptomycin than to isoniazid. The survey did not, however, differentiate between white and immigrant patients. The British Tuberculosis Association 1960–1 survey<sup>5</sup> of acquired resistance also included a control group of 171 new patients of unspecified ethnic origin, in which 11.1% had primary resistance. The second national survey, in 1963,<sup>2</sup> showed primary resistance to isoniazid, streptomycin and *p*-aminosalicylic

acid—either to one drug or to a combination—in 4.4% of patients. Ethnic groups were identified; patients living in the UK from birth had a 3% rate of primary resistance, rising to 7% in Indian and to 11% in Pakistani patients. No bacteriological or drug sensitivity data were recorded in the 1965 BTA survey<sup>6</sup> or the 1971 British Thoracic and Tuberculosis Association survey.<sup>11</sup> The 1978–9 MRC Tuberculosis and Chest Diseases Unit survey<sup>3</sup> included details of primary resistance. White patients had a 1.6% rate of primary resistance and patients from the Indian subcontinent 7.5%, all of them to isoniazid or streptomycin or both. The 1983 survey by the MRC unit<sup>4</sup> showed primary resistance in 1.7% of white patients and 13.1% of patients from the Indian subcontinent. In the latter resistance was to isoniazid or streptomycin or both. In white patients resistance was to isoniazid or streptomycin or both, with one case of ethambutol resistance. The Blackburn figures for these years are compared with those from the published cross sectional surveys in table 6.

In the years 1960–1 there were very few patients from the Indian subcontinent who had tuberculosis in

Table 3 Primary drug resistance in white patients in 1960–84

Period	Total patients	H	S	P	HS	HP	SP	HSP	% Isoniazid resistance
1960–4	341	13	9	1	4	3	1	2	6.5
1965–9	184	4	4	2	2	3	—	1	5.4
1970–4	147	4	2	—	1	—	—	—	3.4
1975–9	124	2	2	1	—	—	—	—	1.6
1980–4	81	—	—	—	—	—	—	—	—

H—isoniazid; S—streptomycin; P—*p*-aminosalicylic acid; R—rifampicin; E—ethambutol.

Table 4 Primary drug resistance in immigrant patients in 1960–84

Period	Total patients	H	S	P	HS	HP	SP	HSP	% Isoniazid resistance
1960–4	38	—	1	—	—	—	—	—	—
1965–9	87	2	3	1	5	1	—	—	9.2
1970–4	165	4	10	2	4	3	—	—	6.7
1975–9	136	5	6	—	3	—	—	1	6.6
1980–4	99	1	9	—	4	—	—	1	6.1

Abbreviations as in table 3.

Table 5 Acquired drug resistance in white patients in 1960–84

Period	Total patients	H	S	P	HS	HP	SP	HSP	Other
1960–4	28	2	5	—	5	2	—	2	—
1965–9	45	8	2	2	1	6	—	2	—
1970–4	14	3	—	1	1	—	1	—	HRE-1
1975–9	3	—	—	—	—	—	—	—	SR-1
1980–4	7	—	1	—	—	—	—	—	—

Only five cases of acquired drug resistance occurred in the immigrant group (1971—H; 1976—RH; 1979—R; 1981—RH; 1984—SH). Abbreviations as in table 3.

Table 6 National rates for primary resistance in *Mycobacterium tuberculosis* (rates for Blackburn shown in parentheses)

	1960-1 <sup>5</sup>	1963 <sup>2</sup>	1978-9 <sup>3</sup>	1983 <sup>4</sup>
Overall (%)	11.1 (12.7)	4.4 (5.0)	2.8 (6.5)	4.3 (9.1)
White (%)	—	3.8 (5.7)	1.6 (2.2)	1.7 (0)
Indian subcontinent (%)	—	9.0 (0)	7.5 (9.5)	13.1 (14.3)

Blackburn. The incidence of primary resistance locally agreed well with the incidence in the control group of the BTA survey,<sup>5</sup> although this was much higher than that found in the 1955-6<sup>1</sup> or 1963<sup>2</sup> surveys. In Blackburn the main rise in the number of patients from the Indian subcontinent occurred after 1963, so that the small numbers of these patients makes comparison difficult for this group; but the incidence in the white population was 50% above the national average. The figures for the separate groups in both 1978-9 and 1983 agree closely with the figures from the MRC unit's surveys for those years, the overall figure for Blackburn being greater than the "national" average because of the higher proportion of patients from the Indian subcontinent in Blackburn than in England and Wales as a whole.

The only survey of acquired resistance was conducted in 1960-1 by the BTA.<sup>5</sup> This showed that 81.7% of "old" patients were resistant to one or more drugs. The resistance rate was highest in patients whose tuberculosis was notified during 1950-5, before good chemotherapeutic practice had been established. Of patients whose disease was notified in 1956-8, however, 79% still had acquired resistance and of those notified in 1959 50% had acquired resistance. The rates of drug resistance varied greatly from clinic to clinic. In some only 2% of patients on the register had acquired resistance; other clinics had an incidence of up to 20%. The survey also showed significant discrepancies in the reporting of resistance by local and central microbiology laboratories, with a discrepancy for isoniazid of 18% for sensitive strains and 17% for resistant strains, for streptomycin of 15% and 13%, and for *p*-aminosalicylic acid of 7% and 31%. Since the drug resistances reported in this paper for 1960-71 were those confirmed by the *Mycobacterium* Reference Unit, such a degree of over-reporting of resistances is unlikely in our figures.

From the data in tables 1 and 2 there is certainly no evidence within the Blackburn, Hyndburn, and Ribble Valley District Health Authority that over 25 years the arrival of substantial numbers of immigrants from the Indian subcontinent (currently estimated at 8.4% of the district population) has had any effect on the pattern of drug resistance in the native white population. Both primary and acquired resistances have fallen progressively in every five year period since 1965 in the white population, with only

one case reported in the last five years. The incidence of primary resistance in the immigrant (Indian subcontinent) group has remained largely unaltered over 20 years, and five cases of acquired resistance have occurred. Bacteriophage and other microbiological tests show that the strains of *M. tuberculosis* from white and Asian patients are different with quite distinct patterns of bacteriophage and chemical reaction.<sup>12-14</sup> There is also no evidence from these studies that there was any change in these patterns from 1969<sup>12</sup> to 1977.<sup>14</sup>

The incidence of tuberculosis in Blackburn over the last 25 years has risen from a level consistently below the national average to one of the top 10 highest local authority areas in England and Wales. The pattern of drug resistance over the same period supports the view that there is no evidence of any cross infection between native white and immigrant Indian subcontinent ethnic groups.

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